REMARKS

Claims 15-16, 36, 38-41, 53, 56-70 and 72 have been amended. Claim 37 has been canceled; and claims 43-50, 54-55 and 71 are reiterated. Claims 1-14, 17-35, 42, 51 and 52 were previously cancelled. Claims 73-80 have been added. Upon entry of the amendment, claims 15, 16, 36, 38-41, 43-50, and 53-80 will be pending. No new matter has been added.

Support for the claim amendments can be found, *e.g.*, at page 8, lines 19-25; page 17, lines 11-28; page 18, lines 9-16; page 18, line 29 to page 19, line 23; page 20, line 7 to page 21, line 6; page 21, line 23 to page 23, line 20; and Example 1 at page 31, line 9 to page 40, line 9, and page 43 line 1 to page 47, line 23, of the specification.

The claim amendments and cancellations made herein are for the purpose of expediting prosecution of the instant application and should not be construed as acquiescence to any of the Examiner's rejection.

Applicants note with appreciation the Office's reconsideration and withdrawal the rejection under 35 U.S.C. §112, first paragraph as applied to claims 66-69.

Applicants thank Examiner Noakes for the courtesy of a telephonic interview with Applicants' attorney on February 23, 2009 during which the outstanding rejections under 35 USC §112, first paragraph, and §103 were discussed. Applicants are grateful to the Examiner for her useful suggestions regarding possible claim amendments to obviate the outstanding rejections.

Objection of Claims 39, 63 and 66 for Minor grammatical errors.

The Office objected to claims 39, 63 and 66 because of minor grammatical errors. This objection has been obviated in view of the claim amendments made herein.

Rejection of Claims 15, 16, 36-41, 43-50 and 53-72 under 35 USC § 112, first paragraph Enablement

On page 3 (paragraphs 4-5) and pages 9-15 (paragraph 12) of the Office Action, the Office has rejected claims 15, 16, 36-41, 43-50 and 53-65 under 35 U.S.C. 112, first paragraph,

for scope of enablement. It is noted that this rejection is applied to the pending claims having a step requiring the use of crystals of P-selectin LE, and is not applied to claims 66-72 as these claims are directed to methods of using the structure coordinates only.

Without acquiescing to the Office's position and in the interest of expediting prosecution, claim 15 and its dependencies have been amended to be directed to methods of using structural coordinates only. In particular, these claims, as amended herein, incorporate the step of utilizing the structural coordinates according to Figure 2, 3 or 5 (within the deviation specified), as a way of generating a three-dimensional model of P-selectin LE. Claim 56 and its dependencies have been amended to incorporate the step of providing a three-dimensional structure of P-selectin LE, wherein said the three-dimensional structure was obtained by subjecting a particular crystal comprising P-selectin LE and having the space group and unit cell parameters specified, to x-ray diffraction and collecting data sufficient to determine the three-dimensional structure of said P-selectin LE. Claims directed to methods encompassing the use of the particular crystals disclosed in the instant application have been acknowledged by the Office as being enabled (see Office Action at page 3). Therefore, this aspect of the rejection has been met.

Written Description

On pages 4 (paragraph 6) and 15-16 of the Office Action, the Office has rejected claims 15, 16, 36-41, 43-50 and 53-65 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Office,

> The claims are drawn to in silico methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE comprising SEQ ID Nos: 6, 8 or 9, or those with conservative substitutions thereof. Thus, the claims are intrinsically drawn to a large number of species of P-selectin crystals containing a considerable number of different P-selectin proteins and thus the claims possess a large genus of widely variant crystals of both P-selectin proteins used to make the crystals..

In the interest of expediting prosecution, independent claims 15 (and claims dependent therefrom) have been amended as described above to be directed to methods of using the

structure coordinates of P-selectin LE, according to Figure 2, 3 or 5, within the deviation specified, thereby obviating this aspect of the Office's rejection.

Claim 56 and its dependencies have been amended to incorporate the step of providing a three-dimensional structure of P-selectin LE, wherein said the three-dimensional structure was obtained by subjecting a particular crystal comprising P-selectin LE and having the space group and unit cell parameters specified, to x-ray diffraction and collecting data sufficient to determine the three-dimensional structure of said P-selectin LE. Thus, claim 56 and its dependencies are directed to methods encompassing a step that relies on the use of the particular species of P-selectin LE crystals disclosed in the instant application, thereby obviating this aspect of the rejection.

Thus, Applicants submit that the rejection of claims 15 and 56 (and claims dependent therefrom) for lack of written description has been met.

In another aspect of the written description rejection (page 6 of the Office Action), the Office has rejected claims 66-72 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Office objects to the use of the phrase "relative structural coordinates" of P-selecting LE in the claims as allegedly encompassing:

> [A] wide and variable genus of distinct three-dimensional structural coordinates sets (e.g. species) which are not limited to Figures 2- 5 by any means, wherein said Figures are the only four species described in the specification. These structural coordinates (Figs. 2- 5), however, are not considered to be representative species for the wide variation of structures found within the three-dimensional structure genus which includes variable structures derived from protein crystallography, NMR or homology model structures.

In the interest of expediting prosecution, this rejection has been met by deleting the term "relative" from the pending claims. The pending claims have been further amended to clarify that the structural coordinates are derived from x-ray protein crystallography as these claims refer to the x-ray structural coordinates of Figures 2, 3 and 5. It is noted, however, for the record that the x-ray coordinates of Figures 2-5 may be modified, *e.g.*, by inversion or integer addition or subtraction, so long as the relative relationship between the coordinates remain the same. For example, all the structural coordinates may be shifted by +1 or -1, so long as all the coordinates

are shifted the same way relative to each other. Accordingly, this aspect of the rejection has been met.

In view of the foregoing, Applicants submit that the method claims, as presently pending, specify the use of structural coordinates or particular species of crystal structures of P-selectin LE to more than adequately satisfy the enablement and written description requirements. Accordingly, reconsideration and withdrawal of the claim rejections under 35 U.S.C. 112, first paragraph are respectfully requested.

Rejection of Claims 66-69 and 70-72 under 35 USC §103(a)

Claims 66-69 and 70-72 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Revelle *et al.* (*JBC*, 1996, 271 (27):16160-16170 - cited on the IDS from 10 December 2001) in view of Morris et al. (*J. of Computer-Aided Molecular Design.* 1996. Vol. 10, pp. 293-304 - cited previously on PTO-892 of 7-3-06) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). To support this rejection, the Office states that:

> Thus, inputting any three-dimensional structure coordinates into a computer program which has specifically been designed to perform this function, does not make the data which is input into said program patentable nor does it make a method of inputting the data into a known program to perform its known and designed function patentable.
>
> Thus, despite that fact that Revelle et al. does not teach Figures 2, 3 or 5, all of the arguments are drawn to the deficiency that Revelle et al. does not teach the requisite data and that Morris et al. does not remedy this deficiency. However, given that this data has been asserted to be non-functional descriptive material, it does not have to be taught in the prior art to establish a case of *prima facie* obviousness. Furthermore, it is noted that Morris et al. do cure some of the noted deficiencies of Revelle et al., namely they do teach a well known computer program designed specifically to perform the rational drug design methods described in the specification.

This rejection is respectfully traversed. Claims 66-72 are directed to methods of identifying candidate agents that interacts with P-selectin LE by using the x-ray structural coordinates according to Figure 2, 3 or 5, within a deviation specified, to generate a three-dimensional representation of the active site of P-selectin LE. The claims further require the

three-dimensional representation to have selected structural coordinates of residues of the active site of P-selectin LE (*e.g.*, amino acids TYR44, SER46, SER47, TYR48, ALA77, ASP78, ASN79, GLU80, PRO81, ASN82, ASN83, ARG85, GLU88, CYS90, GLU92, ILE93, TYR94, LYS96, SER97, PRO98, SER99, ALA100, TRP104, ASN105, ASP106, GLU107, HIS108, LYS111, and LYS113 according to Figure 3; or amino acids SER6, THR7, LYS8, ALA9, TYR10, SER11, TYR44, TYR45, SER46, SER47, TYR48, TYR49, TRP50, ALA77, ASP78, ASN79, GLU80, PRO81, ASN82, ASN83, LYS84, ARG85, ASN86, ASN87, GLU88, CYS90, GLU92, ILE93, TYR94, ILE95, LYS96, SER97, PRO98, SER99, ALA100, TRP104, ASN105, ASP106, GLU107, HIS108, CYS109, LEU110, LYS111, LYS112, LYS113, and HIS114 according to Figure 5). Applicants submit that the claims require the use of three-dimensional representations of the active site of P-selectin LE that were not taught or suggested in the art prior to the present invention. These representations provide valuable insights into the ligand recognition by P-selectin LE, and the design of new agents that interfere and/or modulate P-selectin function.

For example, the instant application provides in Paragraph 91 of US 04/0096894 that:

> Comparing the E- and P-LE/SLe^X structures to structures of related lectin/glycan complexes reveals important similarities and differences. Examination of the crystal structure of MBP-A bound to oligomannose (Weis et al., 1992) indicates a similar arrangement of calcium-binding interactions also involving the 3- and 4-hydroxyl groups of the ligating mannose residue. However, the Fuc ring in the E- and P-LE/ SLe^X structures is "flipped" relative to mannose in the MBP-A/oligomannose complex. This results in the swapping of ring positions so that the Fuc 3- and 4-hydroxyl groups of the selectin LE/ SLe^X complexes occupy the 4- and 3-hydroxyl group positions, respectively, of mannose in the MBP-A/oligomannose complex. Even though different hydroxyl groups are used and their relationship to the sugar ring differs (equatorial-equatorial for the mannose 3- and 4-hydroxyl groups, respectively, versus equatorial-axial in Fuc), the vectors along the sugar ring carbons to hydroxyl groups are maintained. This precise positioning of hydroxyl groups appears to be essential for simultaneous ligation to the calcium ion and hydrogen bond interactions with the protein. The crystal structure of the K3 mutant of MBP-A in which three selectin residues have been introduced (Ng and Weis, 1997) binds SLe^X significantly differently than we observe here for the selectin LE/ SLe^X complexes. While this structure and the structures presented here show Fuc ligation to the bound calcium, different hydroxyl groups are involved. In the K3 mutant/ SLe^X complex, Fuc 2- and 3-hydroxyl groups ligate calcium and occupy the Fuc 4- and 3-hydroxyl group positions, respectively, found in the selectin LE/ SLe^X complexes. This

results in a 90.degree. rotation of the SLe^X orientation within the binding pocket relative to the selectin LE/ SLe^X complexes and affords a hydrogen bond interaction between the Gal 4-hydroxyl group and the side chain of Lys-111, which we do not observe. This highlights the importance of Glu-92, Tyr-94, and Tyr-48 (and Arg-97 in E-selectin) to the binding of the ligand in the E- and P-LE/ SLe^X complexes. Finally, models of SLe^X molecularly docked into the E-selectin lec/EGF crystal structure (Graves et al., 1994; Kogan et al., 1995; Poppe et al., 1997) compare favorably to our results in terms of the general orientation of SLe^X on the binding surface. However all disagree to varying degrees with the structures shown here with regard to the identity of the molecular contacts. With the underlying assumption that ligation of SLe^X to the bound calcium mimics that which is observed in the MBP-A/oligomannose complex and in the MBP-A K3 mutant/ SLe^X complex, all models propose that the Fuc 2- and 3-hydroxyl groups of SLe^X ligate the bound calcium. This is in sharp contrast to our observations of two separate selectin LE/ SLe^X complexes in which Fuc ligation is mediated via the 3- and 4-hydroxyl groups. Other proposed contacts for the E-selectin/ SLe^X interaction are consistent or inconsistent with our results to varying degrees. The design of SLe^X mimetics intended for therapeutic purposes based upon these incorrect structural considerations may ultimately limit the success of these efforts.
Applicants conclude in Paragraph 101 of US 04/0096894:

The crystal structures of P-LE and E-LE complexed with SLe^X and of P-LE complexed with the PSGL-1 sulfoglycopeptide shown here contribute significantly to our understanding of the molecular basis of selectin recognition. The structures of P-LE and E-LE complexed with SLe^X exhibit both common and dissimilar binding interactions, which explain their differential affinity for this shared ligand. The structure of the P-LE/SGP-3 complex in particular illustrates how the differential recognition of PSGL-1 by E- and P-selectin is achieved. While the primary sequences of E- and P-selectin lectin domains are more than 50% identical, residues critical for the P-LE/SGP-3 interaction are unique to P-selectin and presumably account for the higher affinity of the P-selectin/PSGL-1 interaction. Residues Arg-85 and His-114, important for ionic interactions with tyrosine sulfate residues within SGP-3, are unique to P-selectin (the corresponding residues in human E-selectin are uncharged Gln and Leu, respectively). Interestingly, this trend in differential charge at these positions is observed for P-selectin and E-selectin in the mouse, rat, rabbit and cow suggesting a conserved binding motif for P-selectin interactions with PSGL-1.

The present invention provides detailed structural analysis of P-selectin LE in apo and complexed forms. As quoted above, as a result of the invention, new and non-obvious interactions of the active site of P-selectin LE with its ligands, SLe_X and PSGL, were discovered. The residues involved in these newly discovered interactions of the active site of P-selectin LE (for example, residues Glu92, Tyr94 and Tyr48 of the P-selectin LE/SLe_X and residues Arg85

and His114 of the P-selectin LE/PSGL) are embodied by the structural coordinates of Figures 2, 3 or 5, and are explicitly required by claim 66 and its dependencies. Absent Applicants disclosure, the structural analysis of P-selectin and its interaction with its ligands was simply not available in the art. The particular P-selectin crystals that led to the structural analysis embodied by Figures 2, 3 or 5 were not available in the art, and are a result of the present invention. The structural analysis Applicants provided embodied by the structural coordinates and three-dimensional representations recited by the claims do translate into concrete active steps in identifying new candidate agents that interact with and/or modulate P-selectin function.

The art cited by the Office does not render the present claims obvious. As acknowledged by the Office, the primary reference by Revelle *et al.* is simply a review of the effects of various mutations in E- and P-selectin in determining carbohydrate binding specificity. There is no teaching or suggestion in this reference regarding crystals of P-selectin LE (let alone the particular crystals used to derive the structural coordinates recited by the claims), three dimensional structures or models of the active site of P-selectin LE, let alone a method for identifying P-selectin LE using particular x-ray structural coordinates of P-selectin LE, alone or complexed with its physiological ligands. The secondary reference of Morris *et al.* fails to make up for the deficiencies in Revelle *et al.* as it simply discloses a general description of software programs for designing and determining potential ligand-protein interactions.

The Office continues to rest this rejection on the conclusion that the "structure coordinate data of Figures 2, 3 and 5 are given no patentable weight as it is considered to be non-functional descriptive material." This aspect of the rejection is respectfully traversed. The claims, as presently pending, require the use of x-ray three-dimensional coordinates of the active site of P-selectin LE in concrete steps in a method of identifying a candidate agent that interacts with P-selectin LE. The structural details and differences in the active site of P-selectin described in the quoted passage above, were not in any way recognized by Revelle in combination with the secondary references, and are a direct result of the crystals disclosed in the present application. These structural coordinates are used in generating a three-dimensional model of the active site of P-selectin LE; and evaluating the fit between the three-dimensional model of the active site and a candidate agent. These steps do alter the steps performed by a computer program and/or

the drug screens, which ultimately results in the identification of the candidate agent. Thus, the structural coordinates of the active site of P-selectin LE recited in the claims dictate how the in silico and physical screens for P-selectin binding agents are performed..

Therefore, the structural coordinates of the active site of P-selectin LE specified by the claimed methods impart functionality by changing the processing steps of the computer program, changing the structural coordinates of the active site of P-selectin LE and the candidate agent, which ultimately imposes a change in the identification process that leads to obtaining an agent that interacts with P-selectin LE. Such structural information is not non-functional descriptive materials, as alleged by the Office, as it imparts a series of concrete steps having a functional relationship between matter and substrate. See *In re Gulack*, 703 F.2d at 1387.

Accordingly, reconsideration and withdrawal of the present rejection under 35 U.S.C. §103(a) are respectfully requested.

CONCLUSION

In view of the claim amendments and arguments made herein, reconsideration is respectfully requested. The Examiner is invited to contact the Applicants' representative at the telephone number listed below.

A request for an extension of time is submitted herewith. If there is any additional fee occasioned by this Amendment, including an extension fee, that is not otherwise covered, please charge any deficiency to Deposit Account No. 50/2762, Ref. W2025-700110.

Respectfully submitted,
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